Summary

Modelling to explore the potential impact of asymptomatic human infections on transmission and dynamics of African sleeping sickness

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1 Objective

The current incidence of gHAT case reporting across Africa have now fallen to historic lows, leading to some optimism that elimination is within sight.

There is evidence of asymptomatic human infection for gHAT, both as "skin-only" infections, for which parasites are found in skin but not in blood, and other infections (ranging from completely asympatomatic to mildly symptomatic) in those who could be detected during active screening campaigns through confirmed blood parasitemia and may be able to self-cure.

In that respect, the importance of asymptomatic infections for the spread of the infection and the elimination goals remains a relevant concern. Whilst people with confirmed blood parasites are eligible for current treatment, those without will be missed and could constitute an infection reservoir. In this study, we develop a mathematical model to analyse the potential impact of asymptomatic infection by explicit modelling of infection progressing which allows for skin-only parasite infections and self-cure from early stage infection.

2 Methods

The novel model presented here to study asymptomatic infections of gHAT dynamics is based on a baseline model presented originally by Rock *et al.* [1] and updated by Crump *et al.* [2] that takes into account different subpopulations of humans and tsetse. To account for asymptomatic infections, we modify this model by considering two subgroups within the first stage infected humans, labeled as skin parasite I_{1H}^s and blood parasite I_{1H}^b populations. Therefore, exposed population are assumed to develop either parasite infection with detectable levels of parasites in the blood (with probability p_{bs}) or skin-only parasite infection (with probability $1 - p_{bs}$). We assume skin-only infections are asymptomatic, and would not be diagnosed in active screening within the current protocols due to the lack of parasite in their blood (even if these infected people may test positive in initial screening tests such as the card agglutination test for trypanosomes (CATT) or in rapid diagnostic tests (RDTs) based on antibody expression). We take into account asymptomatic cases in blood parasite group as well. As the main difference, this group will be likely diagnosed in active screening if tested (according to the sensitivity of the algorithm used – which is usually considered to be over 90%). In the novel model, we add the possibility of self-cure for both the skin-only and blood parasite groups through the parameters ω_H^b for blood and ω_H^s for skin-only. A schematic of the possible infection progression and transmission to tsetse is shown in Figure 1

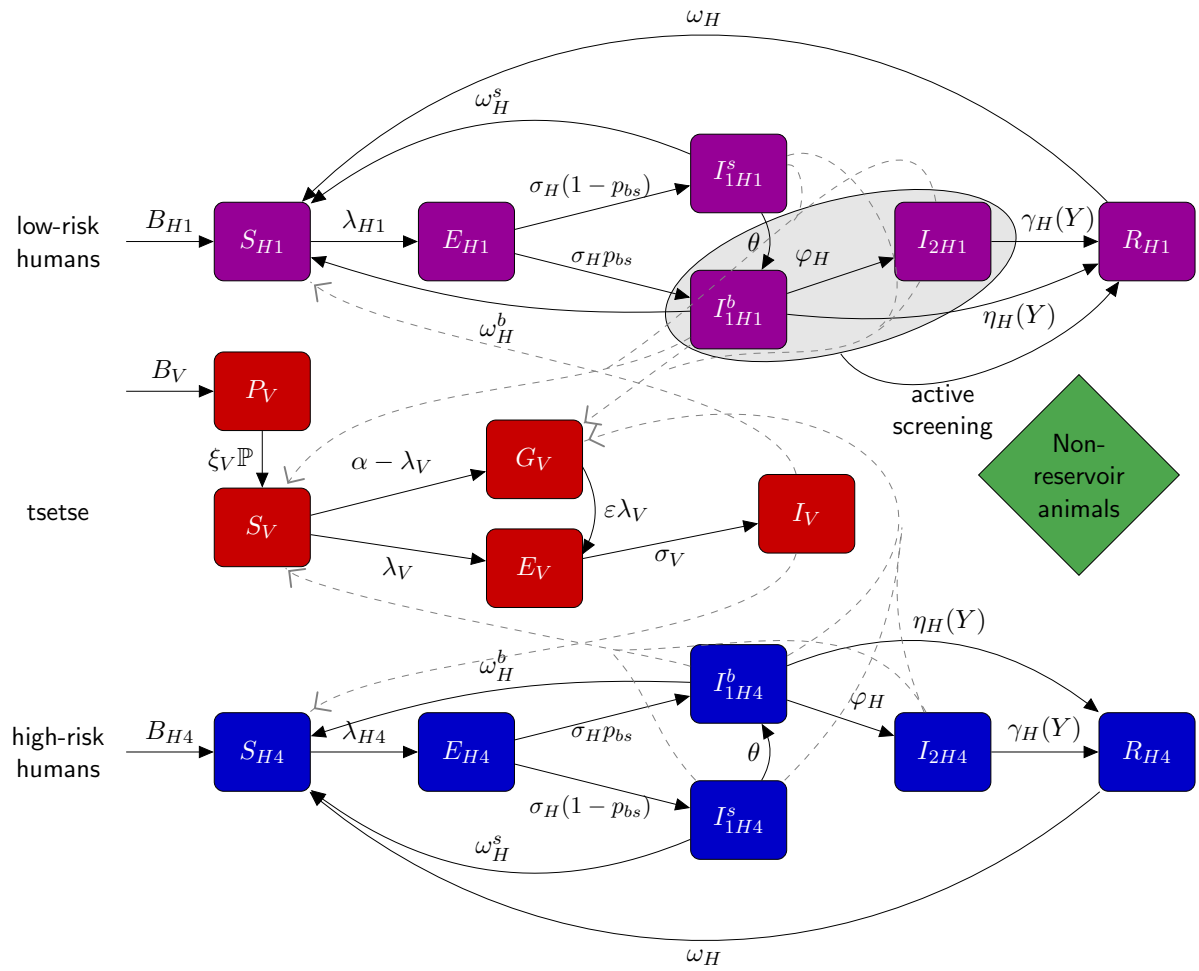

Figure 1: **Schematic of the model to describe gHAT infection dynamics.** This multi-host model of HAT takes into account high- and low-risk groups of humans and their interactions with tsetse vectors. Each group consists of different compartments: Susceptible humans S_{Hi} can become exposed on a bite of an infectious tsetse. Exposed people E_{Hi} progress to become the skin parasite I^s_{1Hi} or blood parasite stage 1 infection I^s_{1Hi}; the latter eventually develops stage 2 (if not detected in screening), and once treated they recover by hospitalisation R_{Hi}. Active screening can accelerate treatment rate of infected people, but only in those with detectable blood infection and in the low-risk group – I^b_{1H1} and I_{2H1}. This is marked on the diagram as a grey box. Here we assume high-risk group does not participate in active screening. By biting an infectious person, tsetse can become exposed and subsequently infectious, E_V and I_V. G_V represents the tsetse population not exposed to *Trypanosoma brucei gambiense* in the first blood-meal and are therefore less susceptible in the following meals. Rates are shown by Greek letters associated with arrows. Animal reservoir is not considered. This figure is a modified version of the original one [1, 2].

Table 1: Model parameters. Notation, description, and a plausible range of values that the five parameters that are new to this asymptomatic model variant could take.

Notation	Description	Range	Unit
p_{bs}	Proportion of exposures resulting in initial blood infection	0.7 [0.4, 0.99]	-
ω_H^b	Self-cure rate of blood infections	[0, 10]$\times 10^{-5}$	days^{-1}
ω_H^s	Self-cure rate of skin-only infections	[1, 10]$\times 10^{-4}$	days^{-1}
θ	Transition rate from skin-only infection to blood infection	[1, 5]$\times 10^{-4}$	days^{-1}
x	Relative infectiousness of a skin-only infection compared to a blood infection	[0, 1]	-

Table 1 presents all the extra parameters introduced in our asymptomatic model that, in addition to all parameters of the baseline model, characterise the infection dynamics within this framework. Considering the nature of asymptomatic infection, it is not straight-forward to quantify the corresponding parameters. We therefore consider broad intervals for their values.

Results

To explore the role of the additional parameters, we first perform multivariate sensitivity analysis of this model, by simulataneously drawing random samples for all model parameters within their plausible ranges to investigate model behaviour (see Table 1). This analysis indicates which parameters are most important to understand and fit, whereas the less sensitive model parameters or ones we have very strong belief about could be left at a fixed value in subsequent modelling work.

Our sensitivity analysis results suggest the extra parameters corresponding to asymptomatic infections can potentially play a significant role in infection dynamics, as is demonstrated by Figure 2 which ranks the model parameters by order of sensitivity. It highlights that the choice of fixed and fitted model parameters used in other studies was a rational choice (all the blue bars denoting previously fitted parameters are ranked higher than grey bars denoting fixed model parameters), and that parameters associate with the probability of initially developing blood infection (p_{bs}), self-cure rate of skin-only infections (ω_H^s) and the relative infectiousness of skin-only infections to blood infections (x) could have substantive impact on model dynamics and should be included in future model fitting.

We study the role of asymptomatic infection on gHAT dynamics by numerically solving our system of equations including annual active screening, which is able to detect asymptomatic infections with blood-parasites but not skin parasites. Active screening also only identifies people in the low-risk group, as we assume high-risk individuals do not participate in active screening (as per previous studies [1,2]). We compare the results of the baseline model with the asymptomatic model for three cases by looking at the total prevalence and reported cases. Figure 3 shows the results for a 20% probability of initially developing skin-only infection (this is an illustrative example to demonstrate model dynamics, however it seems likely that skin-only infections are less common than blood infections). The model is run under one of three cases:

- the basic reproduction number, R_0, is fixed for all simulations. i.e. the average number of secondary infections created with no control in place is the same for all simulations
- The observable stage 2 passive detection incidence is fixed for 1998 for all simulations
- The effective tsetse density is the same for all simulations.

Under each case we see the asymptomatic infection changes the slope of prevalence decline significantly even when skin-only infected people have lower comparative infectiousness to those with

blood infections ($x = 0.2$). This can potentially change the time to reach a threshold of elimination. The effects can be seen more severely in case 3. In this scenario, the prevalence is high and it does not align to the reductions generally observed in case data. However, it does highlight that there are potentially plausible parameter values resulting in an initial drop off in infection, followed by a plateau at a new, lower endemic equilibrium rather than converging to zero.

In a subsequent study we intend to fit this novel model with all extra parameters to the available data to have a more realistic conclusion of the impact of asymptomatic infections on gHAT dynamics.

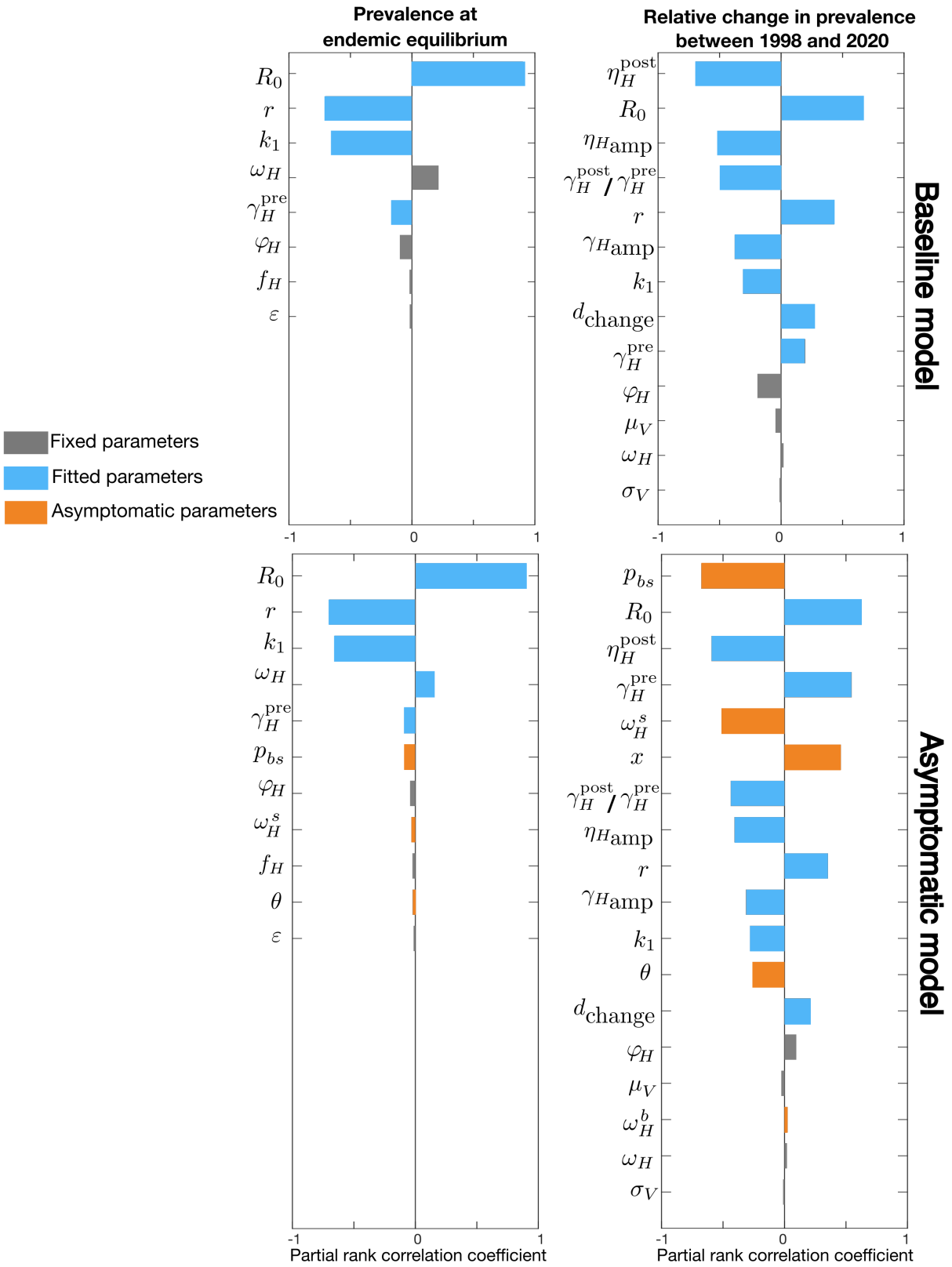

Figure 2: **Sensitivity analysis in terms of model parameters.** Sensitivity of total human prevalence, I_H/N_H, analysed for the whole parameter space of the baseline model (first row) and the asymptomatic model (second row). The first column corresponds to the endemic equilibrium configuration, I_H^0/N_H, and second column represents the relative change in prevalence between 1998 and 2020, $I_H(2020)/I_H^0$. We do not show parameters with sensitivity values below 1% and sort the parameters by their absolute sensitivity value in each plot. Fixed, fitted, and asymptomatic parameters are shown in dark gray, blue, and orange respectively.

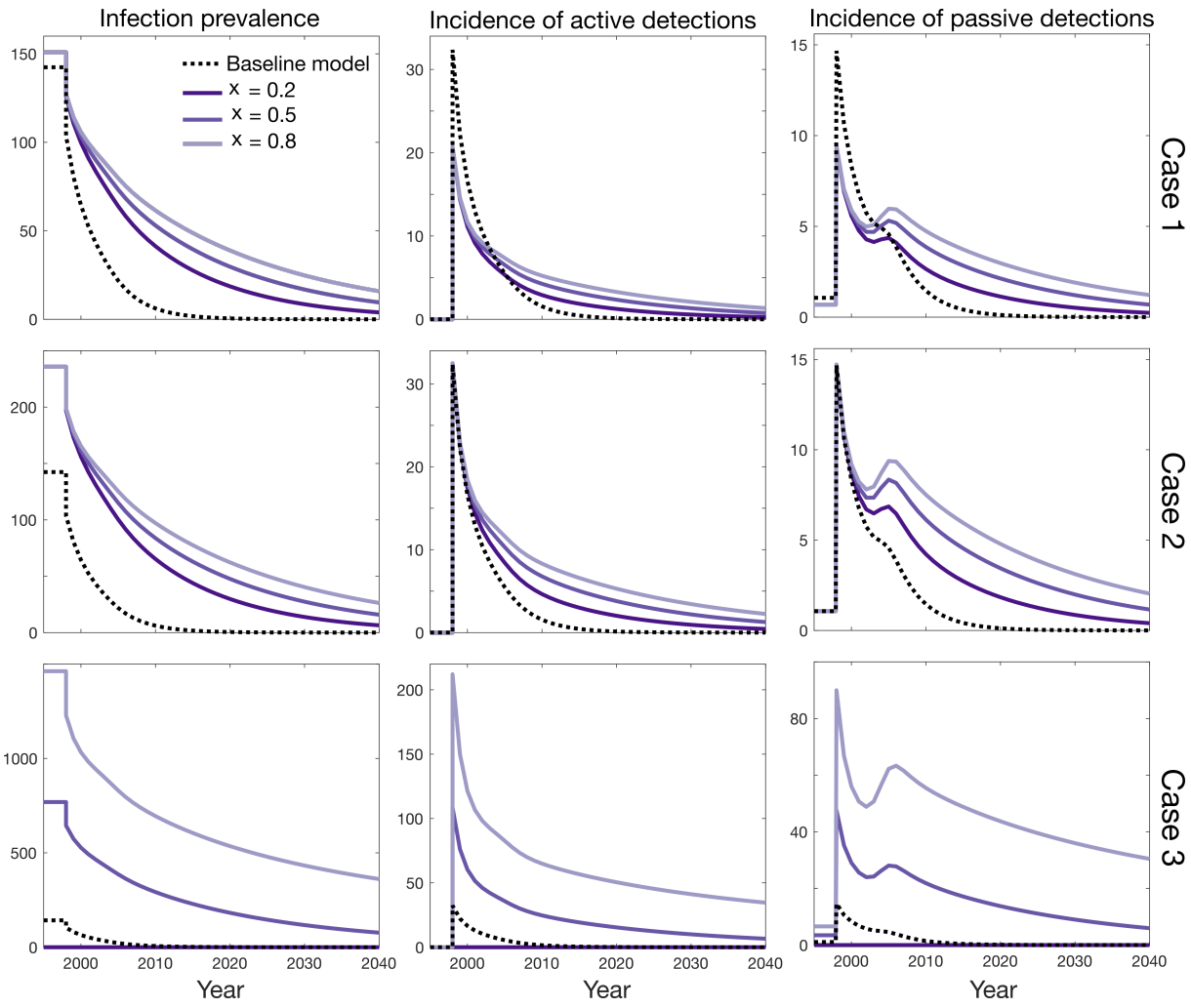

Figure 3: **Influence of asymptomatic infection on infection dynamics.** Total prevalence (per 10,000), active cases reported (without false-positive), and passive cases reported are plotted over the years 1998 to 2100. Each row corresponds to fixing either: (case 1) the basic reproduction number, R_0, (case 2) the observable incidence of passive detections, or (case 3) the effective tsetse density, m_{eff}. Different purple shades represent different values of relative infectiousness of skin-only infection, x, when $p_{bs} = 0.8$, $\theta = 10^{-4}$, $\omega_H^b = 10^{-5}$, and $\omega_H^s = 2 \times 10^{-4}$ are fixed. The baseline model is shown as a dashed black line in each subplot ($p_{bs} = 0$ and $\omega_H^b = 0$).

Acknowledgments

Whilst no human case data were specifically used in this study, the results presented relied on previous model fitting [2], which utilised data collected from the Democratic Republic of Congo (DRC). The authors thank Programme National de Lutte contre la Trypanosomiase Humaine Africaine (PNLTHA) of DRC and its director Dr Erick Mwamba Miaka for original data collection and WHO for data access (in the framework of the WHO HAT Atlas [3]).

References

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